REMARKS

Substance of the Interview

Applicants thank Examiner Blumel for the helpful telephonic interview on June 25, 2008 with Applicants' representatives, Laura Coruzzi and Jennifer Chheda, during which the newly presented claims and amendments that were filed with the Amendment dated April 11, 2008, were discussed.

Claims

Claims 79-96 are pending and under examination in this application. With this amendment, claim 79 is amended to recite " . . . a truncated NS1 protein consisting essentially of amino acid residues 1 to 99 . . . " (underlined text replaces the term "composed of"). This amendment is fully supported by the specification as originally filed. For example, see the specification at page 18, lines 9-10, which states that the truncated NS1 protein can have "from 1-100 amino acids, and preferably 99 amino acids; from 1-100 amino acids . . . ."

Applicants respectfully note that the invention as claimed is drawn to attenuated influenza viruses that have an impaired interferon (IFN) antagonist phenotype. In other words, the genetically engineered viruses used in the invention induce an IFN response in the infected host, and have an impaired ability to down-regulate or counteract the host's IFN response to infection. For example, these viruses can induce higher levels of IFN expression in an infected host than their counterpart influenza viruses that encode wild-type NS1.

Upon entry of this Amendment, claims 79-96 will be pending in this application. Entry of this Amendment and consideration of the remarks below is respectfully requested.

The Rejections Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

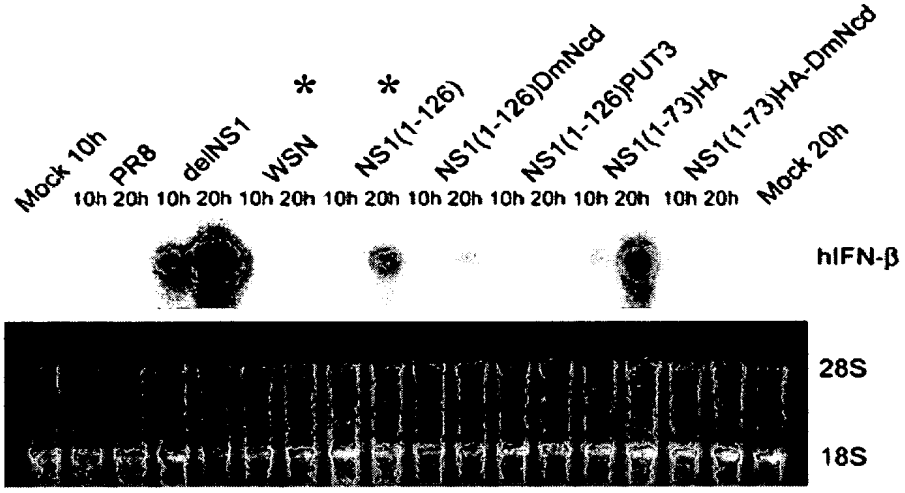
I. Written Description Requirement

Claims 79 and 81-96 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

Although the Examiner has acknowledged that the specification describes the successful generation of an influenza virus with an impaired IFN antagonist phenotype by truncating NS1 to contain only the first 99 amino acids and that the specification describes influenza viruses with other C-terminus truncated NS1 proteins, the Examiner has alleged that Applicants were not in possession of the claimed invention in view of the unpredictability in the art, the breadth of the claims, and the reduction to practice of only one example of a mutant virus in the specification (Office Action at p. 3 to p.4). The Examiner's allegation of the unpredictability in the art is based on two references, Ferko *et al.*, 2004, *J. Virol.* 78:13037-13045 ("Ferko") and Wang *et al.*, 2002, *J. Virol.* 76:12951-12962 ("Wang"), as demonstrating that a mutant influenza virus expressing a truncated NS1 protein of 1 to 125 or 1 to 126 "did not impair the ability of NS1 to down regulate IFN expression" (Office Action at p. 3 to p.4).

Applicants submit that reliance on these references is misplaced, and that contrary to the Examiner's assertion, the mutant influenza viruses described in Ferko and Wang that encode truncated NS1 proteins of 125 and 126 amino acids, respectively, do, indeed, have an *impaired ability to down-regulate IFN expression.* In other words, these mutant influenza viruses induce higher levels of IFN expression in the host than their wild-type counterpart influenza viruses that encode the wild-type NS1 protein.

Wang describes a mutant of the influenza A/WSN/33 virus that encodes a truncated NS1 protein of amino acid residues 1 to 126, which has the ability to induce the expression of IFN-β. Wang states that "infection[s] with . . . WSN-NS1(1-126) viruses, but not with wild-type WSN and PR8 viruses, induced the upregulation of IFN-β mRNA levels in A549 cells" (Wang, p. 12958, 1st paragraph (emphasis added); see also Wang, p. 12960, Fig. 6, which is reproduced below for reference: compare 20h NS1(1-126) lane to the 20h wild-type ("WSN") lane, which are both marked with an asterisk). Importantly, Wang states that the "levels of IFN-β mRNA in cells infected with WSN-NS1(1-126) ... virus[es] correlated with their attenuated properties in mice" (Wang, p. 12953, 1st paragraph of "Results" section; p. 12954, Fig. 1C; and p. 12957 2nd full paragraph and Fig. 2E). Therefore, the NS1(1-126) virus as reported in Wang does, indeed, has an impaired IFN antagonist phenotype.



Ferko describes a mutant of the influenza PR8 virus that encodes a truncated NS1 protein of amino acid residues 1 to 125 which upregulates the expression of IFN-α/β in the serum of mice immunized with the virus. Ferko states that an influenza mutant virus "encoding the 125 amino acids of the NS1 protein (PR8/NS-125 ...) potently induced markedly higher levels of IFN-α/β in mouse serum compared to those induced by the PR8 w.t. virus" (Ferko, p. 13041, 1st full paragraph). This is clearly demonstrated in Table 2 of Ferko (p. 13041), which is reproduced below for reference (highlighted cells – also marked with an asterisk – exemplify the contrast between interferon induction by NS1-125 virus and wild-type virus).

TABLE 2. Peak cytokine levels in serum and mucosal samples of immunized mice[a]

	Cell line	Cytokine level in:			
		Serum (IFN-α/β) (U/ml) at 12 h p.i.[b]		Nasal secretions (pg/ml) at 6 h p.i.	
		i.p.	i.n.	IL-1β	IL-6
	PR8delNS1	16,197	1,387	1,285	502
	PR8/NS1del40-80	19,460[c]	7,322[c]	2,246	2,882
	PR8/NS1-38	8,548	999	1,715	388
	PR8/NS1-80	3,309	<300	1,118	305
*	PR8/NS1-125	24,568	1,642	1,583	401
	PR8/NS1-Nef	25,101	2,955	1,510	320
*	PR8 w.t.	1,691	<300	1,299	522

[a] Mice were immunized with NS1 mutant and the PR8 w.t. viruses. Serum and nasal secretions were collected 6, 12, and 24 h p.i. and then pooled and assessed for the presence of IFN-α/β, IL- 1β, and IL-6 as described in Materials and Methods.

[b] Shown are the peak values of i.p.-immunized mice and i.n.-immunized mice as indicated.

[c] Maximal values were determined already at 6 h p.i.

Moreover, the observed increase in serum IFN correlates with the protective effect of the NS1-125 mutant influenza against challenge with lethal wild-type virus (see Ferko, p. 13041, right column, 3rd full paragraph; and p. 13043, right column, 2nd full paragraph).

Therefore, contrary to the Examiner's assertion, both Ferko and Wang describe mutant influenza viruses encoding C-terminally truncated NS1 proteins that upregulate IFN expression and are protective *in vivo* – *i.e.*, they each have an impaired IFN antagonist phenotype. Accordingly, the Examiner's reliance on these references to support his assertion of unpredictability in "[t]he art of generating an impaired interferon antagonist phenotypic influenza virus, in which the virus has a C-terminus truncated NS1 protein" (Office Action, p. 3) is misplaced.

Accordingly, in view of the present amendment to claim 79 (and claims dependent therefrom) and the remarks above, Applicants believe that the written description rejection is moot, and respectfully request that it be withdrawn.

II. Claims 80 and 85 Are Enabled

Claims 80 and 85 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner states that, if NS1/99 as recited in the claims is a specific strain of influenza virus (which Applicants acknowledge it is), it must "be known and readily available to the public or obtained by a repeatable method set forth in the specification . . . . [but t]he specification does not provide a repeatable method for administering the NS1/99 strain to a host without access to the NS1/99 strain and it does not appear to be readily available material." See paragraph bridging pages 8 and 9 of the Office Action. Therefore, the Examiner states that a deposit of the NS1/99 strain is required for compliance with the enablement requirement..

Applicants note that the requirement to deposit a biological sample does not arise when the sample "can be prepared by one skilled in the art from known materials using the description in the specification." *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 18 U.S.P.Q.2d 1016, 1025 (Fed. Cir. 1991). As stated by the Court in *Amgen*,

> When a biological sample required for the practice of an invention is obtained from nature, the invention may be incapable of being practiced without access to that organism. Hence the deposit is required in that case. On the other hand, when . . . the organism is created by insertion of genetic material into a cell obtained from generally available sources, then all that is required is a description of the best mode and an adequate description of the means of carrying out the invention, not deposit of the cells. *Id.*

The instant application meets this requirement. The specification of the instant application provides a working example that teaches how to make the NS1/99 genetic material from sequences that were known and publicly available, how to introduce it into cells (*e.g.*, MDCK cells and then Vero cells) such that the NS1/99 virus is produced, and how to use this virus in accordance with the claimed methods (see specification at p. 37, l. 8 to p. 41, l. 29).

In particular, the specification teaches that the NS1 gene is obtained from the NS segment of influenza A/PR/8/34 (PR8), the sequence of which was known at the priority date of the instant application (see, *e.g.*, Baez *et al.*, 1980, "Complete nucleotide sequence of the influenza A/PR/8/34 virus NS gene and comparison with the NS genes of the A/Udorn/72 and A/FPV/Rostock/34 strains," *Nucleic Acids Res.* 8:5845-58; reference AR of Information Disclosure Statement filed on November 14, 2003). The specification teaches how to engineer the NS1 gene to make the 99 amino acid C-terminally truncated form, and how to transcribe it using ribonucleoprotein complexes. The ribonucleoprotein complexes are formed by transcription from a linearized plasmid encoding the 99 amino acid C-terminally truncated NS1 in the presence of purified ribonucleoprotein and polymerase of 25A-1 virus, which is a reassortant virus containing the NS segment from the cold-adapted influenza strain A/Leningrad/134/47/57 and the remaining genes from influenza PR8, both of which were publicly available as of the instant filing date. The specification goes on to explain that NS1/99 virus is generated by culturing host cells transfected with the ribonucleoprotein complexes and infected with 25A-1, a temperature-sensitive helper virus. The host cells are incubated for 18 hours at 37 °C and then supernatant containing virus is passaged at 40 °C to select for the NS1/99 virus. Therefore, one of skill in the art would have been able to reproduce the working example in the specification in order to obtain the NS1/99 virus.

Accordingly, contrary to the Examiner's allegation, the NS1/99 virus is obtainable by a repeatable method set forth in the specification and, as such, the specification is enabling for claims 80 and 85 across their entire scope.

Applicants therefore respectfully request the withdrawal of the rejection of claims 80 and 85 under 35 U.S.C. § 112, first paragraph, for lack of enablement.

CONCLUSION

Applicants believe that the present claims meet all the requirements for patentability. Entry of the foregoing amendments and remarks into the file of the application is respectfully requested. Withdrawal of all rejections and consideration of the amended claims are requested.

If any issues remain, the Examiner is urged to telephone the undersigned.

Respectfully submitted,

Date: December 2, 2008

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Enclosure

Accordingly, contrary to the Examiner's allegation, the NS1/99 virus is obtainable by a repeatable method set forth in the specification and, as such, the specification is enabling for claims 80 and 85 across their entire scope.

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